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Please add new Claims 14-15.

--14. (New) A C-type crystal of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester.

15. (New) A granule of the C-type crystal of claim 14 having a particle size ranging from 100 to 1,400 μm.--

REMARKS

Claims 1-15 are pending. Applicants have amended the specification as suggested by the Examiner. Support for the amendment of Claim 1 is found at page 4, line 7 and in Fig. 2 of the specification which describe (C-type) crystals having a specific X-ray diffraction peak at 7.1°. Support for the amendment of Claim 2 is found in the specification, fifth line from the bottom of page 2 and by Fig. 1 which describe (A-type) crystals having a specific X-ray diffraction peak at 6.0°. New Claims 14 and 15 find support in the first paragraph on page 4 of the disclosure, which describe C-type crystals and granules of C-type crystals. Accordingly, the Applicants do not believe that any new matter has been introduced.

Specification/Priority

The Official Action indicates that the Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120. However, the Preliminary Amendment filed along with this application amends page 1 of the specification to indicate that this application is a continuation of International Application No. PCT/JP99/02199, filed on April 26, 1999. Accordingly, the Applicants request verification of the receipt and entry of the preliminary amendment and submit that the conditions for priority set forth by 35 U.S.C. §120 have been met.

Objection--Disclosure

Page 10, line 11 of the specification was objected to as being not comprehensible. Applicants have amended this section of the specification as suggested by the Examiner. Accordingly, it is respectfully requested that this objection now be withdrawn.

Brief Description of the Drawings

The disclosure was objected to because the Brief Description of the Drawings was not properly located. Applicants submit that this issue has been addressed by relocation of the Brief Description of the Drawings section..

Rejection - 35 U.S.C. §112, Second Paragraph

Claims 1 and 2 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for using the phrase "at least". Responsive to the Examiner's concerns, the Applicants have deleted this term and simplified the language of these claims. Claim 1 has been simplified to recite the major, distinguishing X-ray diffraction peak for type C crystals (7.1°) and Claim 2 now recited the major, distinguishing X-ray diffraction peak for type A crystals (6.0°). Accordingly, the Applicants respectfully ask the Examiner to withdraw this ground of rejection.

Rejection - 35 U.S.C. §102

Claims 1 to 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Nofre et al, U.S. Patent No. 5,480,668. Nofre et al do not anticipate the crystals of the present invention because the N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester (hereafter "Neotame") crystals of Nofre et al inherently have a different type of crystalline

structure than the crystals of the present invention or contain more water than the crystals of the present invention. That is, the Neotame crystals of Nofre et al are type A crystals, whereas those of the present invention are Type C crystals.

These differences are shown both by the experimental data in the attached Declaration under 37 C.F.R. 1.132 as well as by the stoichiometric analysis of the yields of Neotame obtained by Nofre et al shown below.

The experimental data presented in the attached declaration shows that crystals produced or recrystallized using the procedures described by Nofre et al are A-type crystals having a major X-ray diffraction peak at 6.0°. On the other hand, the C-type crystals of the present invention, have a major X-ray diffraction peak at 7.1° instead of 6.0° (see Fig. 2 in the disclosure). Nofre et al, col. 7, lines 39-51, describe the synthesis and crystallization of Neotame. After synthesis, Neotame is recovered as a gummy precipitate, which is vacuum dried, and recrystallized by one of two methods: from a water/ethanol (1/1) mixture, or from acetonitrile, see col. 7, lines 49-50.

Nofre et al recover Neotame from a methanol solution by removing the methanol under reduced pressure (vacuum) to obtain a dry powder, see col. 7, lines 44-45. Experimental Example 1 in the declaration shows that Neotame powder obtained from a methanol solution after the methanol was removed by vacuum distillation is an amorphous powder which does not show a clear diffractive X-ray pattern (see Fig. 1 of the declaration).

Experimental Example 2 in the declaration shows that A-type crystals are obtained after dissolving Neotame powder in saline and drying for 2 hrs under reduced pressure, see Figs. 2 and 3 in the declaration, which show a major X-ray diffraction peak at 6.0° characteristic of A-type crystals.

Experimental Examples 3 and 4 show that recrystallization of Neotame powder in

either ethanol/water (1/1) or acetonitrile, see col. 7, lines 49-50 of Nofre et al, and drying of the resulting crystals also produces A-type crystals as shown by Figs. 4-5 (from acetonitrile) or Figs. 6-7 (from ethanol/water).

These results show that the procedures of Nofre et al produce A-type crystals with their characteristic X-ray diffraction peak at 6.0° and not the C-type crystals of the present invention.

Moreover, a stoichiometric analysis of the results reported by Nofre et al indicates that the Nofre crystals contain between 3% and 5% water, and thus would be A-type crystals. On the other hand, the novel C-type crystals of the present invention form when the water content of A-type crystals is reduced to less than 3%, see the disclosure, page 3, line 16.

The water content of the crystals produced by Nofre et al may be determined from the yield value described by Nofre et al in col. 7, line 50 and from the molecular weights of aspartame (294.31) and Neotame (378.47). The process of Nofre et al produced 9 grams of Neotame from 36.2 mmol. aspartame, col. 7, lines 41 and 49. The yield obtained was 62%, i.e. 22.4 mmol. of Neotame was produced from 36.2 mmol. of aspartame (62% yield = 22.4 mmol Neotame/36.2 mmol aspartame). The total weight of the 62% yield (i.e. 22.4 mmol) of Neotame was 9 grams, see col. 7, line 49.

However, 22.4 mmol. of Neotame only weighs 8.48 gr. That is: $22.4 * 10^{-3}$ mol. x 378.47 gr/mol. = 8.48 grams. Therefore, it follows that the Neotame produced by Nofre et al contains 0.52 gr. of water, i.e. the water of crystallization. The amount of water is calculated to be about 5.78% (0.52/ 9.0 grams). A-type crystals contain 3 to 6% water, whereas the C-type crystals of the present invention contain less than 3% water.

Additionally, Nofre et al would not render the C-type crystals of the present invention obvious, as there is no suggestion to produce C-type crystals or any suggestion that C-type

crystals would have improved dissolution rate (solubility) compared to A-type crystals.

Accordingly, the Applicants respectfully ask the Examiner to withdraw this ground of rejection, as both the experimental data present in the declaration and a stoichiometric analysis of Nofre's own results indicates that the prior art crystals are A-type crystals as shown by their X-ray diffraction patterns and by their deduced water content.

Wakamatsu et al, U.S. Patent 4,810,818

In the recent telephone discussion, the Examiner indicated the Wakamatsu et al might be applied as prior art. This document is not directed to N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester ("Neotame") but to a process for producing dry crystals of α-aspartyl-L-phenylalanine methyl ester ("aspartame"). This document does not suggest producing Type C crystals of Neotame, or suggest that Type C crystals of Neotame would have improved dissolution or solubility. Accordingly, the Applicants submit that this document would not anticipate or render obvious the claimed invention.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully request allowance of Claims 1 to 15. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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Docket No.: 197759US0 CONT
Serial No: 09/708,006
Amendment Filed: 09/21/01

IN THE SPECIFICATION

Please amend the specification as follows:

Page 6, between lines 19 and 20, insert:

--BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: a powder X-ray diffraction pattern of A-type crystals.

Figure 2: a powder X-ray diffraction pattern of C-type crystals.--

Page 9, replace the paragraph beginning at line 21 with the following:

--Test Example 1: Measurement of the dissolution rate for the dried crystals

The dissolution rates of the A-type crystals (Reference Example 2 (b)) and the C-type crystals (Example 1) were determined in the following method. That is, 300 mg each of the crystals were introduced into a tabletting mortar (tablet machine) with an internal diameter of 8 mm and a depth of 12 mm, and tabletted at 300 kg/cm2G with "High Pressure Jack J-1 type" (manufactured by Iuchi Seieido) to prepare a sample for measurement of dissolution rate. For measurement of the dissolution rate, the tabletting mortar with only the tabletting face exposed was introduced into 300 ml ion exchanged water kept at 20°C at a stirring [in the number of revolution] rate of 200 rpm, and the inherent dissolution rate was determined using "DISSOLUTION TESTER" (NTR-6100) (manufactured by Toyama Sangyo K. K.).--

On page 12 of the specification, delete the paragraph on lines 15 through 19:

[BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: A powder X-ray diffraction pattern of A-type crystals.

FIG. 2: A powder X-ray diffraction pattern of C-type crystals.]

IN THE CLAIMS

Please amend the claims as follows:

--1. (Amended) A crystal of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester showing a characteristic X-ray diffraction peak [peaks in diffractive X-ray] at a diffraction angle[s] (2θ, CuKα ray) of [at least] about 7.1°[, 19.8°, 17.3° and 17.7°].

2. (Amended) A process for producing the crystal according to claim 1, which comprises drying N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester showing a characteristic X-ray diffraction peak [peaks in diffractive X-ray] at a diffraction angle[s] (2θ, CuKα ray) of [at least] about 6.0°[, 24.8° 8.2° and 16.5°] until its water content is reduced to less than 3% by weight.

3. (Amended) A granule of the crystal of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester according to claim 1, having a particle size [in the range of] ranging from 100 to 1,400 μm.

4. (Amended) A granule according to Claim 3 having a particle size ranging [in the range of] from 100 to 500 μm.--

Please add new Claims 14-15.

--14. (New)

15. (New).--

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